In Reply

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Lung-protective Role of Halogenated Anesthetics

Is It Time to Change This Hypothesis?

To the Editor:

We read with great interest the results of the multicenter randomized controlled trial by Beck-Schimmer *et al.*[1] We congratulate the authors on performing the first study with sufficient statistical power to detect differences in outcomes between two anesthetic techniques in lung resection surgery. The authors used a recognized anesthetic agent (desflurane) with protective (antiinflammatory) lung effects during one-lung ventilation (OLV), although they did not measure perioperative biomarkers of inflammatory response. Most previous hypotheses proposed that this lung-protective role must affect postoperative outcome; however, the surprising results of the study by Beck-Schimmer *et al.*[1] lead us to think that it is perhaps time to reevaluate these hypotheses.

We would like to point out a series of issues that might strengthen the conclusions of this study and could be beneficial for future studies. First, we believe that it is important to report the amount of fluids administered during surgery and the airway pressures during OLV in both groups because an association between these variables and postoperative lung injury has been demonstrated. Second, the authors did not provide data about the depth of anesthesia. Did they use the bispectral index to maintain a similar grade of hypnosis in both groups? The study sample comprised mainly cancer patients, in whom the minimum alveolar concentration of inhaled anesthetics is lower than in noncancer patients. The percentage of desflurane needed to maintain suitable hypnosis could be different. Furthermore, the authors did not show hemodynamic parameters. Can the authors ensure that the *triple low* (recognized variable that could affect outcome) values were similar between groups? Third, in parts of the article, the authors base their findings on volatile anesthesia. We think that they should specify which volatile agent was used. The effects of volatile agents differ, and the differences could have an impact on outcome. We believe that the authors should have avoided the general term volatile anesthesia and stated that their results were obtained with desflurane. The bronchodilator effects of volatile anesthetics differ from one drug to another and provide the anesthetist with useful information, especially in the case of patients with hyperreactivity. However, several investigations show that with desflurane, bronchodilator effects could disappear when the minimal alveolar concentration is greater than 1, whereas with other volatile agents, such as sevoflurane, bronchodilator properties are not dose-dependent.[2,3] This observation could prove to be very important in chronic obstructive pulmonary disease and smokers. Second, experimental and clinical studies have shown that desflurane has less antioxidant power[4–6] than other inhaled agents; the role of oxidative stress in postoperative lung injury during OLV is well known. The same research group previously showed better postoperative outcome after lung resection surgery when they compared sevoflurane with propofol.[7]

Competing Interests

The authors declare no competing interests.

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In Reply:

We would like to thank de la Gala *et al.* for their interest in this clinical trial.

First, the authors raise a concern about differences between the groups in amount of fluids given and the depth of anesthesia. It is important for any trial in perioperative pulmonary medicine to set rules for volume management, hemodynamics, and plateau pressure during ventilation as potential confounders in the study protocol. We were well

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aware of this issue and therefore established a detailed protocol for the study centers with only very few protocol violations as reported. In this large trial with 460 patients, we trusted the power of randomization to eliminate differences in these covariates between the two study arms.[1] As a consequence, we are not concerned about the issues raised by the authors of the letter. The same argumentation applies to the Bispectral Index. The protocol instructed investigators to achieve Bispectral Index values of 40 to 60.

Second, the authors are concerned that we subsume the effect of desflurane under volatiles in general. As described in the letter, differences in clinical effects of the different volatile anesthetics do exist and of course we acknowledge this. Also, different antioxidant properties of volatile anesthetics have been described, which at the same time can also be attributed to propofol depending on the formulation and addition of EDTA.[2] However, it was not our intent to compare different volatile anesthetics. Based on previous findings by our group, we do indeed assume that all halogenated anesthetics with trifluorinated carbon (–CF3) groups provide protection.[3,4] It remains an interesting question if our results could be replicated using sevoflurane instead of desflurane or a different propofol formulation.

Third, the authors address the issue of anesthetics as being lung protective. When discussing protection, it seems key that we clearly define the endpoint of such a protection. As already shown in several randomized controlled trials, the lung itself benefits from a volatile anesthesia, most often through attenuation of inflammatory processes, triggered by ventilation and/or surgical manipulation.[5–7] Based on the result of one of these studies, where patients were shown to have less complications after thoracic surgery with volatile anesthetics,[6] we hypothesized that there would be fewer complications overall for patients in the desflurane arm of our trial. Importantly, the trial of De Conno *et al.*[6] included only 54 patients with surrogate markers as the primary and the clinical outcome as the secondary endpoint. With postoperative complications using a widely accepted classification system as the primary endpoint and an adequately powered approach, our hypothesis was not confirmed with our trial. In conclusion, lung protection provided by anesthetics does not lead to an overall better postoperative outcome. Our trial also highlights the importance of precisely defining study endpoints and proper interpretation. Therefore, we do not think this hypothesis should be reevaluated as proposed by the authors of the letter. In contrast, further trials are needed to test the hypothesis if volatile anesthetics improve complications in the entirely different clinical scenarios of major organ injury such as transplantation, which we did not address in this study.

Competing Interests

The authors declare no competing interests.

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